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Special Article

Ten Medical Myths About FDA

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ONE OF MY first self-imposed tasks after coming to the Food and Drug Administration (FDA) was to search out better ways to communicate with the people who provide care in the health care system. In beginning that search I looked through minutes of meetings held by FDA with physicians and other health care professionals—the ad hoc professional meetings that take place throughout the country. As a result I participated in one as soon as I could.

The questions asked by physicians were of particular interest. They were serious, important, informed. Unfortunately, the information on which some of them were premised—although plausible and widely accepted—would have been more at home in the mythology of Homer than the medicine of Hippocrates.

As I became aware of the mythology quotient, I was reminded of some lines from a Yale commencement speech given by President John F. Kennedy in June 1962. After accepting his own honorary degree and observing that he now had the best of both worlds—a Yale degree and a Harvard education—President Kennedy pointed out that ". . . the great enemy of truth is very often not the lie—deliberate, contrived and dishonest—but the myth, persistent, persuasive and unrealistic."

Real communication between the medical profession and FDA depends upon exorcising several myths about the regulatory process. These myths are pernicious as well as persistent, for they divert the free flow of understanding between those who deliver health care and those who seek to support their efforts.

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Myth Number One. *Drug labeling is FDA's way of telling physicians exactly what they can and cannot do with prescription medicines, and physicians who prescribe for unlisted indications are violating the law.*

Myth Number Two. *In those instances where there is widespread prescribing for an indication not specified in the labeling, FDA seems unwilling or at least insensitive to the need to eliminate the unjustified threat of malpractice litigation by expanding the list of approved indications.*

I group these two myths together because they constitute two aspects of the same problem: myth number one involves legal *status;* myth number two concerns *process.* With regard to the first of these, the plain fact is that FDA approves the accuracy of what is on the official labeling; the physician takes it from there. He or she is responsible for making the final judgment about which, if any, of the available drugs the patient will receive in light of the information contained in the drug labeling and *other available data.*

The law requires that when a new drug is approved for marketing, the conditions of use that the manufacturer or other drug sponsor has *claimed* and *proved* must be set forth in detail in the official labeling. This labeling must accompany the drug in interstate shipment and must contain adequate information for safe and effective use of the drug, including indications; effects; dosages; routes, methods, frequency and duration of administration; contraindications; side effects, and precautions. All of this information is derived from the data submitted with the new drug application.

Once the new drug is marketed the physician may, as part of the practice of medicine, lawfully prescribe a different dosage for his patient, or may otherwise vary the conditions of use from those approved in the package insert—*without*

informing or obtaining approval of the Food and Drug Administration. Although the law does not require a physician to file a notice of claimed exemption for an investigational new drug (IND) before prescribing an approved drug for an indication not specified in the labeling, or to submit to FDA data concerning the therapeutic results and any adverse reactions observed, it is sometimes in the best interests of both physician and public that these things be done.

I know that there are legitimate concerns on the part of physicians that failure to follow the labeling of a drug may be used as evidence of malpractice. Although failure to follow labeling has sometimes been cited as showing a lack of adherence to the usual practice of medicine, it is only one element among many considered by the courts—some of the others being scientific articles, texts and expert opinion. The important consideration is whether departure from approved indications is documented by a legitimate scientific rationale for such use. At this point I must say in all candor that a number of departures that have come to our attention do not appear supportable by any such rationale; to cite but three examples, the prophylactic use of antibiotics postoperatively in uncomplicated sterile surgical procedures, the gross over-prescribing of diethylstilbestrol as a morning-after contraceptive and the misuse of the amphetamines for treatment of obesity.

While there is no magic by which FDA can cause the lag between static labeling and dynamic medicine to vanish, there *is* something we can do to clarify the issue of legal status: spell out the official policy, and give guidelines concerning when it is and when it is not necessary for a physician using a drug for an unlisted indication to file an IND or investigational new drug plan. We are therefore preparing as a matter of top priority a formal policy statement that would clarify officially the legal status of package inserts and provide more specific guidelines to physicians on when an IND must be submitted if a drug is used for research purposes.

What about the other problem: FDA's failure to expand the list of indications even when, it seems, prescribing for an indication is widespread?

One example often cited in this regard is the labeling of propranolol, which was criticized for being confined to use in arrhythmias, hypertrophic subaortic stenosis and pheochromocytoma, at a time when a number of physicians had reported using propranolol with good result in other disorders, notably angina pectoris and later hypertension. When FDA approves a new indication, the law requires that we approve it on the basis of "adequate and well controlled trials" providing scientific evidence that the drug is useful for the specific indication. If the drug sponsor—or anyone else for that matter—does not submit evidence of this kind, there is simply no way we can approve such indications, and no way to flex regulatory muscle to force the sponsor to do the often expensive research necessary.

Even though a particular indication not listed on the insert is widely recognized as appropriate by physicians, so much so that failure to prescribe for it might be considered not in a patient's best interest, the drug sponsor, not FDA, has the legally designated responsibility to produce the controlled trials needed to support the new indication. In such instances, it is far better for physicians to light a candle under the drug company than to curse the darkness in FDA.

In summary, physicians should support FDA's efforts at clarification; but they should *also* monitor their own prescribing behavior carefully, because unjustifiable out-of-label prescription is, in my view, the biggest single invitation to the regulation of medical practice itself.

Myth Number Three. *Since the 1962 drug Amendments to FDA's basic law (which require proof of efficacy), a "drug lag" has been produced. This drug lag is serving to deny Americans important new drugs available in other nations with less restrictive or dilatory regulatory agencies. Further, the cost of the regulation that has produced this drug lag far exceeds the benefits that are being denied to the American people.*

American pharmacology is the most creative in the world, not least in its ability to take inert materials and transform them into brilliant slogans. Among these, "drug lag" may be the most creative. It conveys a concept of a structural, endemic hiatus between drug development and drug marketing, rather than quantitative differences in the drug approval rate between specific countries. Those who argue for the reality of the kind of regulatory climate that would account for the gap between United States and foreign drug approval rates that would affect all drugs, point first to a collection of statistics, and then hypothesize causes for them. We, in turn, produce what we consider a more accurate set of num-

bers. But such statistical tugs of war, involving parties at interest, serve only to confuse and continue the debate.

Two steps have been needed to clear the air. The first is an effort by FDA to eliminate bureaucratic inertia in the drug approval process, particularly for drugs offering high potential value. This has been undertaken, and largely accomplished. Second has been the need for an objective assessment of the drug lag issue. Fortunately, in May of this year, the *Final Report* of the most massive external investigation of FDA ever undertaken provided precisely this kind of objective study. This report, by the Review Panel on New Drug Evaluation, concluded that evidence supporting the drug lag claims is deficient in a number of important respects.

The *Report* cites two major lines of argument by proponents of the drug lag hypothesis. One stems from a study by several physicians who analyzed drugs that were not available here but were available in other countries. This study concluded that the American public had been denied significant drugs due to the costs and delays involved in FDA enforcement of the law. The *Report* finds this contention unpersuasive because "it is unclear whether the drugs referred to in these studies represent significant advances over drugs available in the United States. Moreover, insufficient weight appears to have been given to adverse reactions from drugs marketed abroad which are not available here."

The second argument revolves around a cost-benefit analysis of the 1962 Amendments by Sam Peltzman, Professor of Business Economics, University of Chicago. After applying such analytical techniques to the Amendments, Professor Peltzman concluded that they were responsible for the gross statistical decline in post-1962 drug innovations, and that the costs of drug regulation far outweighed benefits. The *Report* found major methodological and conceptual difficulties with the Peltzman approach; the critique is worth quoting at some length:

> . . . the study used consumer demand theory uncritically and assumed rational economic behavior without accounting for major imperfections in the pricing mechanisms for drugs, such as the fact that decisions to select a drug are made by physicians, not consumers, and are based largely on medical rather than economic considerations. The study also failed to account adequately for the fact that therapeutic areas may differ significantly in their states of technological development and in their trade-offs between safety and benefit. Moreover, while the study used data from the 1950's and 1960's to assess levels of drug innovation before and after the 1962 Amendments, it is doubtful that data for the 1950's should be considered indicative of the "no regulation" situation, because the late 1950's marked the end of a period of unusually active drug innovation resulting from earlier scientific breakthroughs. In addition, although drug approvals declined after 1962, data indicate the decline began earlier. Furthermore, the 1962 Amendments were implemented gradually and their full impact was not felt until the 1970's. Finally, there are important limitations on the use of cost-benefit analysis to study the impact of drug regulation, since cost-benefit analysis entails attaching monetary values to noncommercial health effects, such as death and deformities.

I would hope that we will now spend less time arguing about this particular piece of political pharmacology, and get on with the main business as rapidly as possible. That business, plainly, is to be an effective regulator of techology transfer: watching the public safety carefully, but keeping equally careful account of the foregone benefits of innovation.

Myth Number Four. *Even though there may not in fact be a drug lag in the sense that important therapies are available elsewhere but not in the United States, there is no doubt that drug development is uneven, with certain drugs being developed and made available to patients in other countries before they are marketed here. Hence, the only way for a physician to get certain drugs for patients is to send the patients overseas.*

There appears to be little realization that the way in which drugs are regulated is bound up with something far more fundamental: the way our society has decided to organize itself in regard to business and government. By congressional design, our drug laws flow from, and to a major degree support, the free enterprise system. If a new drug found to be therapeutically important in other countries is not marketed here, FDA cannot force a drug company to apply for permission to market; neither can it do the research itself. These decisions are made by industry in accordance with prevailing commercial incentives.

Dramatic stories of persons traveling overseas to get investigational drugs have left the impression that this is the only way to secure such drugs. The fact is that physicians can often get investigational drugs for their patients by referral of patients to centers where the drug is being tested. If this does not seem practical, individual physicians can also request their own IND's from FDA or from the drug sponsor for drugs that are in the final phase of clinical investigation.

Sodium valproate offers a good example of this

misunderstanding, and it may be useful to trace steps the Agency has taken to improve the availability of this drug in the United States. In November 1976, FDA advised some two dozen new drug sponsors that their products were considered likely to be either a major or a significant therapeutic advance, and that priority attention would therefore be accorded any applications for such drugs. Among them was sodium valproate. In July 1977 FDA went as far as it could under the law: it suggested that the drug's sponsor, Abbott Laboratories, submit an NDA promptly so that the application could be taken before the Agency's Neuropharmacology Drug Advisory Committee in October 1977. FDA also made it clear that, as with other important new drugs, the Agency would consider approving sodium valproate for limited indications, if that was warranted by the scientific evidence, provided that the sponsor agreed to present additional data after marketing. Abbott subsequently advised FDA that it would supply the drug to physicians with patients who have serious cases of epilepsy that may be specifically aided by the drug. Physicians with such patients should apply to Abbott for permission to study the drug under the company's IND. Such use requires the patient to follow the protocol devised by Abbott and FDA.

Myth Number Five. *FDA, through the mechanism of the patient package insert, is seeking to insinuate itself into the physician-patient relationship.*

FDA *is* committed to a much greater use of patient package inserts, a plain-language statement of why patients should follow the physician's instructions regarding certain drugs, what the drugs are intended to do, and the risks they entail as well as their benefits. I believe that such inserts are needed for many prescription drugs—not because this offers a fresh new way for bureaucrats to join in what ought to be a dialogue between patient and physician, but for the opposite reason: because it will strengthen and stimulate cooperation by the patient with the therapeutic efforts of the physician. The fact is that today health care is too often a spectator sport for the patient. What should be of intense interest is too often a matter of passive acquiescence, because the therapy is made to seem too complex and mysterious for lay comprehension. The most cursory glance at the statistics of health outcomes of cigarette smoking, obesity, lack of exercise, excess alcohol consumption—together with the epidemic of noncompliance with prescription information that has been documented by the medical literature—point to the need for people to undertake more responsibility for their own health.

One way in which an agency such as FDA can make a contribution toward dealing with this lack of knowledge, without heavy-handed intervention or large expenditures of public monies, is through better information to patients. This may be the most cost-effective form of medical education we can practice; it supports efforts by physicians, in conjunction with pharmacists and other allied health professionals, to increase knowledge and, thereby, responsibility.

Myth Number Six. *Given the nature of our economy, our legislative and legal process, and our health care delivery system, the way drugs are presently approved is probably the best way that can be devised.*

The present system of drug regulation has served us well, but it is by no means the best that can be devised. Over the years a number of deficiencies have emerged—some minor, some of basic importance. Many of these deficiencies have been brought to our attention by the medical community; others we have isolated ourselves; still others have gained the attention of Congress, or of informed critics of the way FDA operates. Drug law revision is plainly an idea whose time has come. Recommendations for improving the regulatory system made by the Health, Education, and Welfare Review Panel on New Drug Regulation, by FDA to the Administration and in congressional testimony, and through various congressional initiatives seem sure to coalesce into basic reform. There is now a detectable consensus about the direction such reform will take:

- There are likely to be changes that will permit greater flexibility in the clinical testing and marketing of drug products, particularly those entities that may represent significantly or urgently sought therapeutic breakthroughs; there will be new authority to control the distribution of particular marketed drugs, and halt their use summarily where necessary if serious and unanticipated adverse reactions appear.
- New provisions will make drug testing and marketing a more integrated and gradual process than it is today, with drugs being used in an increasingly larger number of persons who can

benefit from their effects in decreasingly sophisticated medical settings—beginning with research scientists in the laboratories and going towards family physicians in communities.

The coming revision of our drug regulatory authority will surely eliminate anomalies that confuse almost everyone. We now have a bewildering array of entities: new drugs, antibiotics, old drugs, grandfathered drugs, and others. This medicolegal smorgasbord makes neither regulatory sense nor health sense. I do not believe that the lawyers who devised it, the regulators who struggle to enforce it, or the practitioners who so often despair of diagnosing it, are happy with the present state of affairs.

Myth Number Seven. *Generic prescribing means that physicians will no longer be certain that their patients are receiving drugs of satisfactory quality, and that many will be receiving what are in effect "second class drugs."*

In carrying out the Food, Drug and Cosmetic Act, FDA must require that every dosage form of each drug be formulated and manufactured in such a way as to meet appropriate standards, and to be safe and effective. For some drug products, in addition to evidence that the products meet appropriate physicochemical standards, a necessary part of this assurance is evidence that each active ingredient is bioavailable to a uniform and acceptable degree. There can be no scientific consideration of the quality, safety and effectiveness of a drug product without consideration of the question of bioavailability.

Until comparatively recently, laboratory testing of drugs for potency, content uniformity and disintegration time was considered sufficient to ensure uniform quality for all formulations of the same drug. Experience proved that this assumption was incorrect. Such tests were not a sufficient guarantee that chemically similar drugs are absorbed to the same degree in the human body. For example, differences in formulation—due perhaps to an ingredient designed merely to extend shelf life or improve palatability—might cause one brand of tablet to be absorbed more slowly than another. Such differences in bioavailability have been encountered in a number of important drugs, but our experience shows that this problem is *not* systematically related to whether the drug was of generic or "brand" origin.

To deal with this problem, FDA issued new regulations establishing bioavailability and bioequivalence requirements for new drugs. In addition to describing methods of testing to determine bioavailability, the regulations provide for bioequivalence requirements concerning those specific drugs that have known or potential problems of bioequivalence.

Those bioavailability and bioequivalent regulations form an essential part of the Maximum Allowable Cost (MAC) program under which the government pays under the Medicare and Medicaid programs for certain generic drugs that are available from more than one manufacturer. The important point is that before a Maximum Allowable Cost is assigned to a drug, FDA *must* review all brands of the drug, and all manufacturers, to ensure that all products meet equivalent standards and that there is no regulatory problem sufficient to prevent a MAC price from being assigned.

Myth Number Eight. *FDA, according to one of the many college classmates now practicing medicine who have recently rediscovered me, is "eliminating many proven standard medications," and following a practice designed "to eliminate a medication when a particular person or committee finds it ineffective—[a policy that] will inevitably return us to the formularies of the Middle Ages."*

FDA *has* taken action to eliminate many standard medications because it cannot be shown that they are of proven effectiveness. A bit of background is in order. Both prescription and over-the-counter (OTC) drugs initially approved for marketing between 1938 and 1962 were required to demonstrate safety but not efficacy. In 1962 Congress *required* that these drugs be retroactively reviewed for effectiveness. FDA accordingly initiated an efficacy review, enlisting the best advice it could find in the process: the National Academy of Sciences/National Research Council (NAS/NRC). The NAS/NRC convened expert panels to carry out its task. The NAS/NRC Drug Efficacy Study is estimated to affect about 80 percent of all prescription drugs (most of 512 OTC drug products in the Study have been transferred to a separate OTC Drug Evaluation Project for review).

Implementation of this Drug Efficacy Study is taking place in three broad phases. In phase I, reports received from the Academy were reviewed by FDA and Initial Announcements were published in the *Federal Register* giving effectiveness classifications for all prescription drug products in the study.

During phase II, FDA puts into a final form the classification ratings of all products reviewed. Manufacturers can then submit data to FDA to support claims of effectiveness. FDA evaluates such data and publishes its conclusions. If FDA finds that the drug product lacks evidence of effectiveness for all claims, it formally proposes to remove the drug from the market, and the manufacturer may then request a hearing. If a hearing is denied by FDA, or is held and the judgment to withdraw the drug is sustained, a Final Order is published stating the reasons and withdrawing approval of the New Drug Application (NDA). As a result, unless stayed by court order, the drug must then be removed from the market.

During phase III, FDA carries out surveillance and compliance.

As can be seen from this summary, the procedure can hardly be described as insensitive to the rights of concerned parties. Indeed, the effort consumed in weighing the evidence and in touching every base necessary to ensure due process leaves me surprised that we have made any progress at all. The box score, at this writing, is as follows: of 3,482 drugs studied, final action has been possible on 2,819, of which 2,065 have been found to be effective; 754 noneffective. (If you would like the evidence regarding why your favorite drug was considered ineffective, please write to me and I will see that you get it.)

Instead of moving us back to the formularies of the Middle Ages, this process takes us in the other direction: further from the formularies of the 1860's that caused an exasperated Dr. Oliver Wendell Holmes to write that with the exception of opium, the anesthetics and a few specific remedies, "if the whole *materia medica*, as now used, could be sunk to the bottom of the sea, it would be all the better for mankind—and all the worse for the fishes."

Myth Number Nine. *FDA animal test protocols are unrealistic, with scientifically inappropriate doses being used, for example, to test for carcinogenicity.*

We have to begin from the premise that humans share most basic biological mechanisms with other animals, and that among those mechanisms is that responsible for susceptibility to cancer. With the possible exceptions of arsenic and benzene, *all* known human carcinogens are also carcinogenic in lab animals. In the design of animal experiments, we are faced with the problem that many types of cancer in humans do not show up for 30 years or longer—by which time the small laboratory mammal, along with ten or more generations of its descendants, has passed into history. And, if we are looking for something that causes, say, a cancer in one of every 10,000 persons exposed, it will be necessary to use several times 10,000 animals in the experimental group alone. Yet an incidence of 1/10,000 is the equivalent of 23,000 new cases of cancer in the United States population. There just are not enough laboratories, toxicologists, animal handlers, money or time to do this for each of the thousands of chemicals that must be tested. So, we compensate for the shortness of the test animal's lifespan and the necessary smallness of the sample by compensating on the other end of the test equation: we increase the dose. That rationale is based on substantial experience with the form of the relationship between dose and response. Despite the impression widely held in the lay public, we are not inducing cancer by excess. In such experiments most compounds do *not* turn out to be carcinogenic.

Myth Number Ten. *FDA talks about communication but, like many large organizations, it seems to view communication as a one-way street, with all the messages going outward. For example, FDA seems to ignore observational evidence supplied by physicians.*

The FDA operates a voluntary adverse reaction reporting system and we listen eagerly—though the sounds we hear are sometimes discouragingly faint (in the United States 15 percent of adverse reaction reports come from physicians, and 63 percent from manufacturers—almost the mirror image of the situation in Great Britain). I can assure you that we pay close attention to such adverse drug reaction reports, and that we value them highly. Every single reaction report is reviewed, and there are instances in which a single report has resulted in labeling changes.

FDA is also one of the few agencies of the federal government to hold meetings with physicians and other health professionals. I intend to continue this practice; and I also urge any reader who may have a specific question about why we act as we do, or who may wish more detailed information about any of the subjects discussed in this article, to write to me directly. I will see to it that you get a straight answer.